TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CIRCULATORY SYSTEM DEVICES PANEL

Pages 1 thru 243

Gaithersburg, Maryland
September 11, 2000

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

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CIRCULATORY SYSTEM DEVICES PANEL

10:10 a.m.

Monday, September 11, 2000

Gaithersburg Marriott Washingtonian
Washingtonian Boulevard
Gaithersburg, Maryland

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P A R T I C I P A N T S

Panel Participants

Cynthia M. Tracy, M.D., Acting Chairperson
Megan Moynahan, Executive Secretary

Voting Members

Michael D. Crittenden, M.D.
Julie Freischlag, M.D.

Consultants (with Temporary Voting Status)

Kent R. Bailey, Ph.D.
Melvin L. Griem, M.D.
Geoffrey Ibbott, M.D.
Mitchell Krucoff, M.D.
Kenneth E. Najarian, M.D.
Tony W. Simmons, M.D.
J. Frank Wilson, M.D.

Industry Representative

Gary Jarvis

Guest

Robert L. Ayers, Ph.D.

FDA Participants

James E. Dillard III
Donna-Bea Tillman, Ph.D.
Bram Zuckerman, M.D.
Chris M. Sloan
Kimberly B. Peters
Henry T. Heaton II

C O N T E N T S

P R O C E E D I N G S

ACTING CHAIRPERSON TRACY: Good morning. While we're waiting for our panel to assemble, I'd like to call to order this meeting of the Circulatory System Devices Panel, and our Executive Secretary will read the conflict of interest statement.

MS. MOYNAHAN: The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. The agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants to determine if any conflict exist.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest. However, the agency has determined that the participation of certain members and consultants, the need for whose services outweighs a potential conflict of interest involved, is in the best interest of the government.

Therefore, a waiver has been granted for Dr. Mitchell Krucoff for his interest in a firm that could potentially be affected by the panel's recommendations. A copy of this waiver may be obtained from the agency's Freedom of Information Office, Room 12A15 of the Parklawn

Building.

We would like to note for the record that the agency also took into consideration other matters regarding Drs. Krucoff, Cynthia Tracy, Julie Freischlag, Frank Wilson, and Kenneth Najarian. These panelists reported interests in firms at issue, but in matters that are not related to today's agenda. The agency has determined, therefore, that they may participate fully in all discussions. In the event that the discussions involve any other products or firms not already on the agenda for which an Food, Drug and Cosmetic Act participant has a financial interest, the participant should excuse him- or herself from such involvement, and the exclusion will be noted for the record.

With respect to all participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

ACTING CHAIRPERSON TRACY: All right. At this time I'd like to ask the panel members if they could briefly introduce themselves.

DR. BAILEY: I'm Kent Bailey, Biostatistics at Mayo Clinic.

DR. CRITTENDEN: Michael Crittenden, cardiac surgeon, West Roxbury VA, Harvard Medical School.

DR. SIMMONS: Tony Simmons, Cardiology, Wake Forest University.

DR. IBBOTT: I'm Geoff Ibbott, medical physicist at the University of Kentucky in Lexington.

MS. MOYNAHAN: I'm Megan Moynahan, Executive Secretary of the Circulatory System Devices Panel.

ACTING CHAIRPERSON TRACY: I'm Cynthia Tracy. I'm from Georgetown Hospital, cardiology.

DR. FREISCHLAG: I'm Julie Freischlag, a vascular surgeon from UCLA Medical Center.

DR. KRUCOFF: I'm Mitch Krucoff. I'm a cardiologist at Duke University Medical Center and the director of device clinical trials at the Duke Clinical Research Institute.

DR. WILSON: Frank Wilson. I'm a radiation oncologist, Medical College of Wisconsin, Milwaukee.

DR. NAJARIAN: Ken Najarian, interventional radiologist, University of Vermont.

DR. GRIEM: Mel Griem, University of Chicago, radiologist and radiation biologist.

MR. DILLARD: Jim Dillard. I'm the Director of the Division of Cardiovascular and Respirator Devices at the Food and Drug Administration.

MS. MOYNAHAN: I'd like to briefly mention that Robert Dacy, our consumer representative, won't be participating today. He was hospitalized late last week. And we attempted to find a replacement for him but were unsuccessful. So we'll be proceeding today without Robert Dacy.

I'd like to also read the appointment to temporary voting status for today:

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, as amended April 18, 1999, I appoint the following people as voting members of the Circulatory System Devices Panel for this meeting on September 11, 2000: Cynthia Tracy, Tony Simmons, Kent Bailey, Kenneth Najarian, Frank Wilson, Mitchell Krucoff, Melvin Griem, Geoffrey Ibbott. In addition, I appoint Dr. Cynthia Tracy to act as temporary Chair for the duration of this meeting. For the record, these people are special government employees and are consultants to the panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

It's signed by David W. Feigald, Director of the Center for Devices and Radiological Health.

ACTING CHAIRPERSON TRACY: Okay. We'll move on to the open public hearing. Are there any parties present who would like to make a presentation at this time?

[No response.]

ACTING CHAIRPERSON TRACY: If not, then we'll begin with the sponsor's presentation, and I'd like to remind the speakers to introduce yourselves and to state any conflict of interest.

MR. GREEN: Good morning. My name is Andrew Green, and I'm the Director of Regulatory Affairs for Novoste Corporation. Madam Chairman, panel members, representatives of the FDA, we are pleased today to present to you a review of the data that supports the safety and effectiveness of the Beta-cath system in the treatment of in-stent restenosis.

Today's presentation will include: this overview; a device and procedure summary by Dr. Burton Speiser, a radiation oncologist and investigator in the START trial, as well as the principal investigator in the START 4020 trial; a review of clinical results by Dr. Jeffrey Popma, principal investigator for the START trial; a device performance and training review, again, by Dr. Speiser, investigator in the START trial; a discussion of specific topics by Dr. Kuntz, Director of the Cardiovascular Data Analysis Center, who did the analysis for the START trial; and some concluding remarks by Dr. Popma, the principal investigator.

The Novoste PMA P000018 was submitted on April 17, 2000, and requests approval for the 30 millimeter Beta-cath system, specifically developed for intravascular brachytherapy in the cath lab, in the treatment of in-stent restenosis of native coronary arteries 2.7 to 4 millimeters in diameter. This was a randomized, multi-center, placebo, triple-masked trial for in-stent restenosis for the Beta-cath system.

We believe that the data that will be reviewed today by Drs. Speiser, Popma, and Kuntz will show that the Beta-cath system has demonstrated effectiveness in significant reductions in all clinical and angiographic outcomes, demonstrated safety and significance reductions in major adverse cardiac events without increased risk of thrombosis to patients, and demonstrated ease of use, short treatment times, minimal exposure to patients and staff, allowing the clinicians to stay in close contact with the patients through the duration of the treatment.

At this time I'd like to have Dr. Speiser come up and present the device and procedure summary. He is, again, a radiation oncologist and an investigator in the START trial.

DR. SPEISER: Thank you. Novoste has reimbursed normal travel expenses and as well as paid an honorarium for my meeting attendance.

I'd like to first discuss the use of Strontium-90. Overall, radiation in any form has a fairly long history for proliferative diseases. External radiation has been used to prevent keloid formation and heterotrophic bone formation. Brachytherapy, specifically Strontium-90, has approximately a 50-year history for the treatment of pterygia, a proliferative disorder of the eyes.

The Strontium-90 has been used, as I mentioned, for benign proliferative conditions in the past. The primary mechanism of in-stent restenosis is a proliferative problem in intimal hyperplasia, and the Strontium-90 has an excellent therapeutic ratio, that is, a dose-to-target which is much higher than the dose-to-non-target tissue.

Now, while I'm talking about Strontium-90, in effect, Strontium-90 decays to Yttrium-90, and in the decay of Yttrium-90 to Zirconium, we have an energetic beta particle of 2.27 MeV, and that in effect is the issue(?) that we're using. However, for simplicity, I will be referring only to Strontium-90.

Strontium-90 has some very advantageous features. It has a dose rate which is quite high, providing very short treatment times, in the range of 3 to 5 minutes, a long half-life of 28.8 years, which eliminates the problem associated with frequent source replacement. Its dose penetration is limited, which matches the dose profile needed in the coronary arteries. It then also means that there's minimal exposure to non-target tissues, as defined as tissues greater than 1 cm from the source axis, and the physician is able to stay with the patient during the entire procedure.

This is a graph showing the ISO dose curve with--iridium-192 is the isotope that I most frequently use for brachytherapy and which I have the greatest experience, and in red is the Strontium-90. The bottom is in centimeters, not in millimeters. And what it shows in the shaded area is that in the range of the arteries that we'll be treating, both isotopes provide excellent delivery. The added value for the Strontium-90 is that there's a very rapid dose fall-off, providing extra safety.

Now, the exposure on Strontium-90 to the patient is approximately three-tenths of a millirem per procedure, and that's contrasted to an average dose that they received during the fluoroscopy during the procedure of 350 millirem.

The radiation oncologist and the interventional radiologist or interventional cardiologist receives approximately two-tenths a millirem and 4 to 16 millirem for the fluoroscopy. In addition, the radiation oncologist receives another 4 millirem per procedure hand dose by handling the device both pre- and post-procedure.

Now, the radiation exposure for the patient is quite low. The Strontium-90 component is less than one-tenth of 1 percent of the total dose received during the procedure. The radiation oncologist and interventionalist receive an extremely low dose of the yearly maximum allowable, and the cath lab personnel receive a very tiny dose of their total yearly maximum allowable.

I'd like to go into the Beta-cath system and the procedure as it's used.

Now, the system is an integrated system that contains a source train of Strontium/Yttrium-90 within a transport device which is then mated to a specific delivery catheter, the Beta-cath catheter, and is complemented with different system accessories.

Now, the features of the system is that it's a completely closed system, which allows for controlled delivery and return of the source train such that the sources never make contact with the patient's blood or tissues. In addition, the device has safety interlocks to prevent the sources from inadvertently being discharged from the device unless everything is hooked up completing the closed system. Once again, the treatment time is very short, 3 to 5 minutes, and that allows the physician to remain with the patient during the entire procedure.

Now, the State of Georgia has performed a safety evaluation of the Beta-cath system and has issued a sealed source and device registration certificate August 4th of this year, and this certificate has been included in the

Nuclear Regulatory Commission sealed source and device registry.

Now, the team consists of radiation oncologists, the interventionalist, either the radiologist or cardiologist, a medical physicist, and the complementary cath lab staff.

Now, while the interventionalist is completing the angioplasty, the radiation oncologist, with the aid of the physicist, will prepare the Beta-cath system. And this includes over here putting the device in a sterile bag and attaching the syringe--this is a hydraulic system--then next attaching the delivery catheter, and you prime the system to ensure that there's sufficient fluid in the system before the start of the procedure.

Next is the prescription of the dose and treatment time based on individual assessment of the reference vessel diameter.

Now, the dose is prescribed at 2 millimeters from the center of the source axis, and this is based on individual assessment of the reference vessel diameter. So for an RVD that's equal to or greater than 2.7 millimeters or less than or equal to 3.3, the dose delivered was 18.4 Gray and for the larger vessel it was 23 Gray.

Next, the delivery catheter is placed across the injury site, and this shows the marker bands here and here that on the delivery catheter to aid the interventionalist to place it across the appropriate area. And this is done with the aid of fluoroscopy.

And next is the delivery of radiation, and this is an animation showing the sources coming out hydraulically. Now they're here, there are markers here and here to further assess the placement of the sources. And the source train remains for approximately 3 to 5 minutes, and the placement is checked periodically with fluoroscopy, so you can see the marker here and the marker band on the catheter just outside of that area to ensure that the source train is at the proper position.

In addition, what I'd like to do is, if you can see this arrow over here, there's a light that indicates the amount of pressure. As long as that light or any of the two lights above it are lit, there's proper pressure to maintain the source train at the right position without any source drift. Following the completion, the sources are hydraulically removed back into the transport device.

At that point the radiation oncologist removes the system, which is both the transport device and catheter, and the interventionalist completes the procedure.

I'd like to introduce Dr. Jeffrey Popma, who is the principal investigator for the START trial, who will discuss the clinical results of the trial.

DR. POPMA: Dr. Tracy, panel members--next slide, please?--I have no equity interest in Novoste. I will receive travel expenses but no honorarium for today's meeting.

Next slide, please?

Again, I apologize to Dr. Krucoff, but what I want to do for the non-interventionalist group is to put a little bit of a perspective on where we stand with in-stent restenosis.

We estimate this year that over 725,000 procedures, coronary interventional procedures will be completed in the United States, and in these 725,000 procedures, 80 percent of the patients will receive one or more stents.

Now, stents have been very useful for us in the cath lab to prevent restenosis, but, nevertheless, clinical restenosis still occurs in 10 to 20 percent of patients. And what that means is that over 100,000 patients will develop recurrent symptoms due to in-stent restenosis in the United States this year.

We have several existing treatment options. Most commonly we perform balloon angioplasty, repeat dilatation within the segment. We tried for a while using a stent within a stent, and we were disappointed that that did not prevent recurrence for in-stent restenosis. We've tried

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rotational atherectomy, directional atherectomy, ex-(?) or angioplasty, but to date we've had no randomized trials that have demonstrated that this lowers the frequency for recurrence. And, of course, oftentimes, the patient is left with the option of bypass surgery or in many cases a repeat coronary artery bypass operation because the first one has had some limitations.

Next slide, please?

Now, we have also learned that, depending upon the pattern of restenosis, the recurrence rate will vary. In very focal, discrete lesions, we know from data from Roxanna Mayron (ph) at the Washington Hospital Center that the recurrence rate is 20 percent. However, restenosis often recurs in a much more proliferative pattern, and when the lesion recurs with length more than 10 millimeters, when it's proliferative, or when it's totally occluded, the recurrence rates after treatment of in-stent restenosis range from 35 to 83 percent. It's still a problem.

Now, we have some good randomized trial data that has been done. This is from the ARTIST trial that was reported at the ESC last year, and this was a randomized trial of patients coming into these European investigators' clinical practices where patients either received balloon angioplasty, conventional way of treating patients, or a debulking device, rotational atherectomy. And what was found in this I think was relatively important. The restenosis rates ranged between 51 percent to 64 percent, a slight increase in the restenosis rate with rotational atherectomy, but target vessel revascularizations occurred between a third and a half of patients. So it's still a clinical problem, and we have not fixed this with aggressive debulking therapies.

So the purpose of the START trial was to assess the safety and efficacy of intracoronary beta radiation using a Strontium-90 source train following successful coronary interventions in patients with in-stent restenosis.

I should also emphasize that this is a unique trial design for device trials in that it is a large-scale trial, which was prospectively constructed, including 50 centers, was triple-masked so that the patients, the investigators, as well as the core laboratories did not know which treatment strategy the patient received, and this randomized trial included 476 patients with successfully treated in-stent restenosis. Two hundred and forty-four of these patients were randomized to treatment with Strontium-90, and 232 of these patients were randomized to treatment with placebo.

We'll talk a lot about endpoints, and I'm going to give you some definitions for these endpoints in just a moment. But the primary efficacy endpoint of this trial was

8-month target vessel failure. The secondary efficacy endpoint was 8-month angiographic restenosis, the occurrence of in-stent--the in-stent minimal lumen diameter, and the degree of the late lumen loss within the vessel.

The safety endpoint was the 8-month major adverse cardiac event rate, and the occurrence of a new aneurysm formation.

Let's talk about these definitions, and they will be presented as the primary and secondary endpoints. So I'll ask your patience to move through these.

First of all, the primary endpoint will be target vessel failure, and that's defined as target vessel revascularization, the clinical need for a repeat revascularization procedure, myocardial infarction or death that could not be clearly attributed to a vessel other than the target vessel. Major adverse cardiac events were defined as death, Q wave and non-Q wave myocardial infarction, emergency CABG, and target vessel revascularization.

For this study and all the studies that we do that evaluate restenosis, we used target vessel revascularization as an endpoint, which was defined as any clinically driven repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel. What this means for the patient is the following: They've had a successful treatment. They go home from the hospital. Somewhere between 3 and 6, maybe 8 months later, they develop recurrent symptoms. They have an exercise test that shows that there's a problem with the distribution in the area that was treated. They come back in and they have an angiogram, and the angiogram shows that there's been a significant renarrowing within the area of either the vessel for target vessel revascularization or of the lesion itself when we use the endpoint of target lesion revascularization.

Again, clinically driven, exercise test recurrent symptoms associated with the appropriate anatomy that shows that this is, in fact, clinical restenosis.

This trial was supported by the following individuals: Rick Kuntz ran the data coordinating center; Alexander Lansky ran the core laboratory; Peter Fitzgerald served as the IVUS intravascular core laboratory director; Peter Zimentbaum did the EKG core laboratory.

I think it's very important to emphasize that this study was watched over very carefully with Tom Ryan as the head of the Data and Safety Monitoring Committee. Tom Ryan is a professor of medicine at Boston University and has chaired up some very important Data and Safety Monitoring Committees. I think it's fair to say that he really--with this study and with the Beta-cath trial--has done a very good job, I think, overseeing this very important committee.

The Clinical Events Committee was chaired by Dave Cohen at the Beth Israel Hospital in Boston.

Now, let's put this talk about which patients are going to be included in the study. This study included single lesion, single intervention, where there was a greater than 50 percent narrowing within the previously placed stent. The target vessel diameter needed to be between 2.7 and 4 millimeters in diameter. And we'll talk about this in a bit, but the target lesion length was treatable with a 20-millimeter balloon, in which case we used a 30-millimeter source train, or treatable with a 30-millimeter balloon, in which case we used a 40-millimeter source train, in order to have adequate margins outside the injured area.

The major exclusion criteria were multi-vessel coronary intervention, a target lesion residual stenosis of greater than 30 percent. The patients needed to have a successful procedure before they were entered into this study. Other exclusion criteria included unprotected left main disease and prior chest radiotherapy.

Dr. Speiser has reviewed the dose prescription. It was done visually, and it was 18.4 Gray in reference vessel diameters between 2.4 and 3.3, and 23 Gray in reference vessel diameters between 3.3 and 4 millimeters.

We'll talk about antiplatelet therapy at the initiation of this trial. We felt and left the adjunct antiplatelet therapy to the discretion of the physician.

Now, I also want to stop and say this is adjunct antiplatelet therapy we're talking about. Aspirin was standard therapy in all patients after their intervention. The adjunct antiplatelet therapy that we'll be discussing are drugs like tyclopadine(ph) or clopitogril(ph), and they're given in addition to aspirin therapy. And at the initiation of this protocol, we left that decision to the investigators.

We then learned some important information from Tom Ryan and the Date and Safety Monitoring Committee from the Beta-cath trial and suggested that there might be a benefit in extended antiplatelet therapy in those patients who received a stent. So on March the 19th, we modified the adjunct antiplatelet regimen, and we recommended at that time that there be a minimum of 90 days of adjunct antiplatelet therapy with the placement of a new stent.

The results that you will see today with the 8-month clinical follow-up will comprise 96 percent of patients that were included in the study. This is an updated report from what you have seen in your panel pack. Angiographic follow-up was obtained in over 80 percent of patients, and this is superb for a clinical device trial.

I'll just go through some very basic clinical demographics. Let me just say at the outset that they were balanced in the two groups: age, gender, the presence of diabetes, prior myocardial infarction, prior bypass surgery, all balanced without differences between the two groups.

The reference vessel diameter was 2.77 millimeters and 2.76 millimeters in the two groups, and there was no significant difference in minimal lumen diameter, the pre-procedural percent diameter stenosis, the lesion length, or the percent of vessels that were treated in the left anterior descending artery.

We did use debulking devices frequently to obtain a successful procedure in the study, and rotational atherectomy was used most commonly in approximately 40 percent of patients. We also used stents relatively infrequently. Only 20 percent of patients received a new stent. I think it's important to emphasize that we reserved the new stent use for bail-out indications, and those bail-out indications were for a severe residual stenosis or a dissection that occurred after radiation therapy. So the stents that were placed in the study were placed after radiation therapy had been delivered. Again, you got into the study because you were felt to have a successful procedure.

Now, I'll just go over just very briefly what antiplatelet therapy the patients actually received if there was not a new stent placed. Forty percent of the patients did not receive antiplatelet therapy or that information was not available to us, which means that 60 percent of patients who did not receive a new stent received subduration of antiplatelet therapy. In patients who had a new stent placed, we did not know or there was no antiplatelet therapy given in 8 percent, but the vast majority of patients received antiplatelet therapy most commonly between 1 to 30 days, 11 percent received 30 to 60 days of antiplatelet therapy; another quarter of patients received more than 60 days of antiplatelet therapy.

I'm going to have to take a moment and explain this slide. You're going to see this slide several times, and I think it's going to be important that I just take a moment and try to set the stage.

When restenosis occurs in patients who have a stent, it occurs because there's intimal hyperplasia, tissue growth within the stent. And our conventional method of analyzing that tissue growth is by analyzing the stented segment itself. If tissue grows within the stent, it most commonly occurs within the axial length of the stent, and this is where we would determine our stented segment recurrence rate. So that when we do our conventional analyses, we look at the stented segment itself, and we'll talk about those results, and you'll see percent stenosis and restenosis rates that are specifically confined to the axial length of where the initial stent was placed.

You'll also see a total analysis segment, and that total analysis segment includes a lot of things. It includes along the axial length of the vessel where the stent was. In your panel pack, you'll see that we also have the numbers for where the injury was with the balloon, where the radiation was delivered, but the analysis segment that you'll see will include the stented segment, a little bit longer length with the tissue that's injured, a little bit longer length that had the radiation, and then 5 millimeters both proximal and distal to that will be included then in this longer axial length. And we'll talk more about this in just a minute.

The restenosis rates were significantly reduced within the stented segment, from 41.2 percent to 14.2 percent, a 66-percent reduction. Within the analysis segment, there was also a significant reduction from 45.2 percent to 28.8 percent.

Now, these are the clinical outcome measures within the study. We'll talk about the primary endpoint, target vessel failure, about major adverse clinical event rates, and then the clinical indices of restenosis of target vessel failure and target lesion revascularization. Those are what we use.

There was a 31-percent reduction in target vessel failure, a 31-percent reduction in major adverse clinical event rates, a 34-percent reduction in target vessel revascularization, a 42-percent reduction in target lesion revascularization--again, all the clinical endpoint parameters that we use to demonstrate efficacy in reduction of clinical restenosis.

This is a major adverse event-free survival curve. It shows that the two curves are superimposable out to 90 days. And then at 90 days, which is the typical time course when restenosis occurs, then there's a separation of these curves showing a benefit of Strontium-90 therapy over conventional--placebo-treated patients, and this is a significant difference out to 360 days.

We also need to talk about subacute stent thrombosis, and I want to take a moment and do that. There was one patient in the placebo group who developed subacute stent thrombosis within the first 30 days of the procedure. There was no patient in the treated group that had that event.

Between 31 and 240 days, which is the time endpoint, there were no occurrences of subacute stent thrombosis in either group.

You will hear in just a moment about one patient who had a clinically adjudicated subacute stent thrombosis that occurred at 244 days, and we'll talk about the details of that patient in just a moment.

The angiographic total occlusion rate between the two groups was identical, 3.3 percent versus 3 percent in those treated with placebo. So no differences in the occurrence of late total occlusion at follow-up and no differences between the occurrences of the clinical event of subacute stent thrombosis.

Let's go into the details about the patient who developed the event at 244 days. On March 2, 1999, the patient's mid right coronary artery was successfully treated in the radiation group. Following radiation treatment, a new stent was placed because the clinical investigator identified a dissection. Despite the fact that a new stent was placed, there was a 48-percent residual stenosis within the treated area, within the stented segment by the core angiographical laboratory, and that suggests to us that this was a suboptimal initial treatment.

On 11/1/99, which was 244 days after the treatment, the patient presented with chest pain and EKG changes which were new in posterior-lateral Q waves. The angiogram showed a total occlusion of the mid right coronary artery. The proximal mid right coronary artery then received a balloon angioplasty and additional stent.

Now, there are a lot of issues to something like this, but we were most conservative in how we reported this. And it is not clear to us whether or not this represented progression of disease or a new stent thrombosis, but we're going to classify it in our presentation to you most conservatively as a new stent thrombosis. And to summarize, that means that there was one stent thrombosis in the placebo group that occurred within the first 30 days, and even after the 360 days where we follow up patients now, there's only one additional event that occurred in the Strontium-90-treated group.

Next slide.

Let's talk about the 8-month safety results. There were four deaths in the study--one death in the placebo group and three deaths in the Strontium-90 group. The overall incidence of about 1 percent death rate is what we'd expect for a randomized clinical trial of this size. The occurrence of myocardial infarction, there were seven in the placebo group, four in the Strontium-90-treated group. There was one patient in your panel pack that was classified as having had an aneurysm. When this was reanalyzed by Dr. Lansky in the angiographic core laboratory, it was found that this aneurysm was present at baseline, and it did not significantly change during the follow-up period.

Let's just review very briefly a description of the deaths in this study.

The first patient was a 77-year-old patient who was successfully treated with radiation on 12/7/98. He died 193 days later of complications following surgical resection of a colonic polyp. The causes of death included his longstanding coronary disease, congestive heart failure, and multi-organ system dysfunction.

The next patient was an 83-year-old man who was successfully treated with radiation on 3/4/99. He died 225 days after treatment. The cause of death was metastatic prostate and rectal cancer.

The third patient in the radiation group was an 83-year-old patient who was successfully treated with radiation on 3/5/99. He died 160 days later, two days following a left upper lobectomy for lung cancer. The death was reported as a post-operative myocardial infarction.

The final patient was a 69-year-old patient successfully treated in the placebo group on 1/22/99. He died 102 days after treatment with the official cause of death reported as cardiac arrest.

We'll talk more about some of the specifics of this in just a moment with Dr. Speiser and Dr. Kuntz's next presentations, but I think what we can take home from the START trial is the following: The 8-month clinical outcome summary shows significant reductions in all outcome parameters, which include target vessel failure, major adverse cardiac event rates, target vessel revascularization, target lesion revascularization, and angiographic restenosis. We do not feel that there was an increased risk of thrombosis. There was one subacute thrombosis in the placebo group and conservatively classified one in the Strontium-90-treated patient that occurred at 244 days, and there were no new aneurysm formations found.

What I'd like to do is to turn this back over to Dr. Speiser who will discuss device performance and training programs based on what we found in the START trial.

DR. SPEISER: Thank you.

First, I'd like to briefly go over the device performance. In the START trial, there were 476 patients enrolled. Successful treatment occurred in 467, or 98.1 percent. The causes for unsuccessful treatment were the catheter did not optimally cross the lesion in six patients, or 1.3 percent, and the sources could not be sent in three patients, 0.6 percent.

The minor device malformations I will refer to as MDMs. There were 89 patients that had successful treatment with MDMs. Now, the total of these different reported MDMs here equals greater than 89 because some of the patients had more than one observation. If, however, you look at the source transit time of greater than 5 seconds and the source marker drift, this accounted for approximately 90 percent of the cases.

One of the cases correctly listed here had in your packet been inadvertently categorized as a reported event in the Beta-cath study when, in fact, it was in the START trial. That patient had a reported event but not a mis-administration.

Now, with the observations of these MDMs and experience gleaned from the START trial, Novoste has made device modifications to the Beta-cath system, and those modifications are what was submitted to the FDA in this PMA that is being reviewed. In addition, they were able to create an in-depth training program that incorporates experience specifically from the START trial and have modified the user's manual to include detailed instructions on component connections, pressure tests and monitoring, as well as the manual removal procedure, which is a mandatory procedure for any brachytherapy type of treatment.

Next, briefly I'd like to discuss the training program, and this will consist of regional training where the individuals and team will train on the device, procedures, both the treatment and safety, and the roles and responsibility of each team member. Specifically, there will be a hands-on session with the devices to familiarize everybody with the device and detailed instructions for the individuals and team with specific experience from the various trials. There's also cross-training of team members on terminology and professional fields so that there's no confusion in the cath lab and radiation safety training for everybody involved.

This is then followed by on-site--which means the facility where the device will be used--training and, once again, first will be reinforced the training on the device, the procedures, and roles and responsibilities. Again, detailed instructions will be given a second time. The procedure will be demonstrated, and that in turn will be followed by a mock procedure conducted in the cath lab; and last, but not least, reinforcement of the radiation safety training for all members of the team.

And the last phase of the training program will be a proctored program with an estimate of 3 to 5 procedures that will be proctored to assess the team proficiency with the procedure and system and to advise team and individuals on device use and handling.

I have one slide I'd like to put in for long-term safety. The BERT trial now has four-year follow-up, and in this particular trial, what I'd like to do is to show that approximately from 12 months to 48 months, the curve is flattened out, which would indicate that there are no long-term problems that are currently being seen with the radiation arm.

Thank you.

I'd like to next introduce Dr. Kuntz, who is the Director of CDAC, who will be discussing specific clinical topics relevant to the START trial.

DR. KUNTZ: My name is Rick Kuntz. I'm an interventional cardiologist at Brigham and Women's Hospital. I'm also the Director of the Academic Contract Research Organization at Harvard Medical School which conducted this trial.

I don't have any equity in this company or any other medical device or drug company, and I'm not being paid for my presentation today.

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I'd like to focus on two issues here that I think require further explanation. One is the clinical impact of the minor device malfunctions, and the second is an analysis of the edge effect.

Next slide?

Starting with the MDM analysis, as Dr. Speiser has shown, 87 percent of those patients classified with an MDM had a radiation-related subcategory of either source drift or a prolonged transit time greater than 5 seconds. The remainder of the MDMs, such as inability to deliver the delivery catheters and others, did not deal with radiation issues.

Next slide?

We attempted to try to determine whether the classification of an MDM, as written in the protocol, had any substantial clinical consequences. So the first thing that we did was look at one of the primary endpoints, that is, major adverse cardiac event rates at 240 days, and compare them between those patients classified as having either drift or increased transit time compared to those patients who fit within the guidelines.

This is an analysis of the placebo patients, and remember, nobody knew if they were placebo or radiation, so drift or increased transit time could occur on both sides.

If we look at the placebo group, there was no substantial or significant difference between the incidence of MACE or between those patients classified as having drift or transit time compared to those without.

We then evaluated the same endpoint for patients assigned to the active arm. Again, we found no significant difference in the incidence of MACE between those with drift and transit time MDMs versus those without. However, you'll notice there that there may be trend, that is, that there was a tendency for an increased estimate rate associated with patients with drift or transit time MDMs. The difference that was seen here did not reach statistical significance, but we tried to understand what might explain the trend.

The first thing we evaluated was the component of the MACE that we felt was the actual safety issue, that is, the occurrence of myocardial infarction or death. What we found was that there was absolutely no evidence of an increased risk of MI or death for patients who had been classified as having drift or increased transit time. There were zero events in those classifications compared to those without drift or those that fit the criteria. So 3 percent of these MIs and deaths overall occurred in patients who met the criteria and protocol and zero occurred in those who were classified as having an MDM. Clearly, there is no significant difference here and no evidence that the drift or transit time issue increased the risk of myocardial infarction or deaths.

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So what explains the difference that we see in this? And the difference is explained by the incidence of target vessel revascularization or the other component of MACE. Now, whether that difference is going to be substantial or clinically important or not leads us to conclude that possibly if there is a difference, it was a difference in the efficacy endpoint of restenosis, and that's it, not in the safety issue of death or myocardial infarction.

We can postulate that possibly drift or increased transit time might reduce the overall deliverable radiation effect. It may be--it's something that you can imagine, and maybe that explained the difference in reduction in efficacy. Then, again, there may be no difference at all because the p-value for this is 0.11. But the important point is that when we look at the incidence of major adverse cardiac event rates between these two subsequent applications, we found no evidence that we exposed the patients to an increased risk of a safety endpoint of death and myocardial infarction.

Next slide?

In order to evaluate whether restenosis differences could have occurred because of the tendency for increased target vessel revascularization was evident in that initial analysis, we looked at another measure of restenosis using quantitative angiography. And in this case, we compared the overall restenosis rates of patients using quantitative angiography between those classified without a source drift or transit increase and those with the MDM. We found absolutely no difference in that measure of restenosis overall.

So our conclusion, therefore, is that source drift and source transit greater than 5 seconds were prospectively collected and possibly could have been very conservative measures and potentially ambitious goals, but were still collected as events and identified as primary minor device malfunctions.

The clinical impact of this classification of MDMs demonstrated no statistical difference in any safety measure of the Beta-cath system in the treatment of in-stent restenosis; and, moreover, the sponsor has proposed minor device modifications and training measures to reduce the occurrence of these sort of drifts and transit increases.

The next issue I'd like to address is the issue of edge effect. As you recall, Dr. Popma's presentation demonstrated that all measures of restenosis showed a significant benefit for patients exposed to radiation therapy compared to those exposed to placebo. But the impact was greatest in the analysis that was confined to the stent area compared to the analysis that was liberated to the wide analysis segment. One of the questions is that if we start to see more restenosis on a wider measure of restenosis compared to one confined within the stent, is there any activity occurring at the areas outside the stent that are measured by the analysis? And this has been brought up by many investigators in the past as a potential problem associated with radiation therapy called edge effect. And there have been a lot of postulated ideas that the radiation therapy can cause narrowing itself in areas that aren't treated, and there may be areas termed geographic miss in which the balloon injures the artery and there's a fall-off of radiation that may cause increased narrowing.

So we were very curious to understand whether this analysis was, in fact, accurately depicting edge problems or it was an artifactual result from the limitations of this analysis and may represent nothing at all.

Next slide?

So in order to approach this, we have to review again how the initial analysis is done. As Dr. Popma showed you earlier, this is a conventional analysis that's been used for all coronary treatments in the last 15 or 20 years; that is, we tend to measure restenosis based on the location of the minimum lumen diameter, and that's how conventional angioplasty has been evaluated. So that if we look at patients and measure restenosis defined by narrowing within the stent segment, a quantitative angiographic technique used by Dr. Lansky at the core laboratory would identify the area of most narrowing and would tell us what that narrowing is and tell us where it's located. If that narrowing is greater than 50 percent of some reference value, we call that restenosis.

The other analysis that we can do is to actually measure the minimum lumen diameter across a very wide area. In this case, we called that the analysis segment. Again, we would detect just one single minimum lumen, and we would tell where the location is.

What we found is that if you measure the minimum lumen diameter, it tended to be located in the stent for the vast majority of patients assigned to placebo. If we looked at the minimum lumen diameter for those assigned to active arm, a fair substantial minimum lumens were located outside the stent and not in the stent. So we attempted to understand whether there was an increased propensity for radiation therapy to cause more narrowings outside or if, in fact, we were just unmasking disease that was already there.

Next slide?

So Dr. Lansky re-evaluated the data set with a specific analysis looking at edge effect, and what was done here was that the measurement of restenosis was confined to just the edges of the analysis segment and not the stent itself to specifically address this issue. So at the source end, both proximal and distal, an analysis centered on that end going 5 millimeters on each side was performed in which the minimum lumen diameter was defined, both proximal and distal, and the incidence of restenosis was measured between the two groups. And what she found was that there was no significant difference between restenosis measured both proximally or distally, depending on the assignment of patients to placebo or active arm. And I think this definitively shows that there was no significant increase in edge narrowing seen in patients assigned to radiation therapy.

Next slide?

So the question is how did we get that disparity between our initial analysis, which showed a 66-percent reduction when we measured restenosis within the stent, compared to 36 percent when we measured restenosis within the analysis segment. We think we can understand how that artifact might have occurred.

In a normal vessel that gets treated, most of the narrowing occurs initially within the stent, hence in-stent restenosis. After treatment, we generally clear out the entire lumen with either aggressive balloon angioplasty or debulking device. And then the patient is assigned to either placebo or active therapy with the radiation source train, and then they're followed up six months later to see what happens.

Next slide?

In patients assigned to placebo, what we found was that there was narrowing that occurred normally on the edges and in the middle, but the vast majority of narrowing and the pattern of narrowing occurred mainly within the stent.

And this has been seen in other in-stent trials and even in *de novo* stent lesions; that is, the response of restenosis is a little bit on the edges, and the majority of it occurs within the stent. So when we do analysis of where the minimum lumen diameter is, it tends to occur mainly within the stent for patients assigned to placebo.

In the radiation therapy group, we get the same degree of narrowing on the edges, but a profound reduction in restenosis in the middle because that's where the targeted therapy was. This may be familiar to radiation oncologists with the concept of central control, where once you take care of the central control of a tumor, you may start to realize peripheral disease starts to show up. Very similar concept here in that what we see here is that an effective therapy may unmask the already present narrowing that has occurred is identical between the two groups.

So as Dr. Lansky showed us, the two narrowings and the size were the same, but if you have an effective therapy in the middle, you may unmask the occasional case of patients who have 50-percent narrowing on the sides. So in that analysis you will see that some of the restenosis occurs in the stent and some of it occurs on the side when you have an effective therapy in the middle.

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So the conclusion of the edge analysis is that significant treatment effects seen between the analysis and stent segments was potentially due in part to injury of the radiation therapy or the masking of progression of normal restenosis seen with any cardiac treatment unmasked by effective radiation therapy.

Now, given both of those two possibilities, the data really supports the masking issue of progression of disease rather than an induction of narrowing occurring by radiation therapy.

I think now I'd like to turn the podium over to Dr. Popma to make some conclusionary statements.

DR. POPMA: Go to the next slide.

I think in very rapid sequence you've heard that there is a medical need to treat in-stent restenosis. It is a problem for patients. It's a problem in all of our clinical practices.

What we've demonstrated in this trial are the following: First of all, the START trial was the largest trial of its type that used randomization, used triple-masking, used placebo-controlled to demonstrate its conclusions. And the summary of what we've heard so far was that the pre-specified hypotheses were all achieved with statistical significance. Target vessel failure was reduced by 31 percent. Major adverse clinical events were reduced by 31 percent. Target vessel revascularization was reduced by 34 percent, and target lesion revascularization was reduced by 42 percent.

On the angiographic analysis, we saw that the pre-specified restenosis hypotheses were achieved with statistical significance. Within the stented segment, there was a 66-percent reduction in angiographic restenosis. And with the analysis segment, there was a 36-percent reduction in angiographic restenosis, both highly significant.

We also learned that the treatment with Strontium-90 in the START trial was safe and that there were no differences in the occurrence of death or myocardial infarction between Strontium-90-treated patients and placebo-treated patients.

There were no differences in late thromboses, there were no differences in total occlusions, and there were no differences in the occurrence of new aneurysm formation.

So what we would conclude from this trial is that the Beta-cath system has been shown to be safe and effective for the treatment of in-stent restenosis.

MR. GREEN: That concludes the presentation by Novoste Corporation for the Beta-cath system.

ACTING CHAIRPERSON TRACY: Thank you. I'd like to ask the panel members if they have any brief clarifying questions they want to ask. We'll have much more time later for discussion. Anybody? Any brief question?

[No response.]

ACTING CHAIRPERSON TRACY: Then we'll move on to the FDA presentation.

MS. MOYNAHAN: While FDA is setting up, let me mention that we've been joined by Dr. Robert Ayers of the Nuclear Regulatory Commission. Dr. Ayers will be participating as a guest today, and he is identified as a coregulator of the use and licensing of the Novoste Beta-cath system.

MS. PETERS: Good morning. My name is Kim Peters, and I'm a biomedical engineer in the Interventional Cardiology Branch of the Office of Device Evaluation. I am also the leader reviewer for the Novoste Beta-cath system PMA submission P000018. Today, Dr. Bram Zuckerman, the medical officer for this submission, and I will present the FDA summary for the Beta-cath system.

This presentation will identify the FDA review team members, provide a brief summary of the device description, provide a summary of the non-clinical tests conducted on the Beta-cath system, provide a summary of the clinical investigation of the Beta-cath system, and identify the FDA questions for the panel.

Members of the FDA review team include Dr. Sabu Subramanian and Dr. Bram Zuckerman, both from the Office of

Device Evaluation; Mr. Tom Heaton from the Office of Science and Technology; Mr. Gary Kamer from the Office of Surveillance and Biometrics; and Ms. Marianne Linde from the Office of Compliance.

As described during the sponsor's presentation, the Beta-cath system is comprised of the Beta-cath delivery catheter, the transfer device, the source train, and system accessories. The Beta-cath deliver catheter is a sterile single-use catheter that provides the path through which the source train is delivered to and retrieved from the treatment site. The catheter includes three lumens to allow for the passage of the guide wire, source train, and hydraulic fluid. At the distal end of the catheter, the source train and hydraulic fluid lumens are closed, while the guide wire lumen remains open to the vasculature. The distal end of the catheter also features two radiopaque markers that define the treatment zone of the catheter.

The transfer device stores and shields the source train when not in use and controls the hydraulic delivery and return of the source train during the treatment procedure. The transfer device features a series of components intended to protect the health care workers and patient from unnecessary radiation exposure, either by shielding the source train or maintaining proper position of the source train. The transfer device also features a series of components intended to regulate, direct, and manage the hydraulic fluid that controls the delivery and return of the source train.

The source train consists of a series of individual, cylindrical, sealed radioactive sources with an inactive gold marker at each end of the train. The radioactive sources are Strontium-90 seeds encapsulated in stainless steel.

The system accessories include a procedure accessory pack, an emergency storage container, a response kit, and a medical physicist kit. These components are intended to facilitate the operation of the system during the clinical procedure, permit temporary storage of the system in the event of a disrupted procedure, and facilitate handling of the source train if located outside the system.

The clinical investigation for the Beta-cath system, the START trial, was conducted with the Alpha III and Alpha IV models of the transfer device. Approximately 83 percent of the clinical data was obtained using the Alpha II model, with the remainder of the data being obtained using the Alpha IV model. Modifications were made to the transfer device in response to reports of device malfunctions during the clinical investigation and to improve the system function.

The main difference between the Alpha III and

Alpha IV models is the addition of the LED pressure indicators. The pressure indicators provide feedback to the user regarding the pressure necessary to remain the source train at the treatment zone and to send or return the source train to and from the transfer device. The indicators also advise the user when excessive pressure is being administered.

The Alpha IV revision two model of the transfer device is the subject of the PMA submission. No clinical data was obtained using this model. As noted in the FDA's summary, the Alpha IV revision two model mainly includes refinement to some of the electronic circuitry and indicators. The Alpha IV revision two model also includes a modification to prevent the transfer device gate from inadvertently being locked prior to the delivery of the source train. FDA believes that these modifications can be evaluated through bench testing.

Optional accessories of the Beta-cath system include an introducer sheath and an extension tubing set. Excessive hemostasis valve tightening can restrict the movement of the sources in the Beta-cath system. An optional component, the arrow introducer sheath, may be used to increase the resistance of the catheter to collapse when compressed with the hemostasis valve. The optional extension tubing set provides an additional fluid management system for use during the clinical procedure by allowing two control syringes to be connected to the Beta-cath system.

During the START trial, both the 30-millimeter and 40-millimeter delivery catheters and source trains were used. The difference between the 30-millimeter and 40-millimeter delivery catheters is the marker spacing at the distal end of the catheters. The spacing identifies the treatment zone of the catheter. The difference between the 30-millimeter and 40-millimeter source train is the number of active source seeds. The 30-millimeter source train includes 12 seeds, and the 40-millimeter source train includes 16 seeds.

Due to the limited clinical data available for the 40-millimeter model, only the 30-millimeter delivery catheter and source train are subject of the PMA.

A series of *in vitro* tests were performed to evaluate the mechanical integrity and function of the Beta-cath system and each of the individual components. FDA is working with the sponsor to resolve questions regarding this testing information. The delivery catheter is the only patient-contacting component of the Beta-cath system. Biocompatibility testing completed in accordance with the ISO Standard 10993 demonstrated that the catheter is non-toxic and non-hemolytic.

Electrical safety, battery, and electrode magnetic compatibility tests were conducted in accordance with applicable voluntary standards. All test requirements were met.

As discussed in the FDA summary, the sponsor has conducted two animal studies using both oversize stent injury and balloon overstretch injury pig models. The results of the animal tests show no difference in restenosis between the Beta-cath system and the control.

With regard to the source dosimetry, FDA is working with the sponsor to resolve questions with the dosimetry information and dosimetry labeling recommendations.

The sponsor has provided data from three clinical studies: the Beta Energy Restenosis Trial, the Beta Radiation in Europe Trial, and the Stents in Radiation Therapy Trial. The Beta Energy Restenosis Trial was a U.s. feasibility study evaluating the use of beta radiation following PTCA and *de novo* lesions. Eighty-three subjects were enrolled in the study. The Beta Radiation in Europe Trial is a multi-center, non-randomized registry that is studying the use of the Beta-cath system following PTCA or stenting of *de novo* lesions. One hundred fifty patients were enrolled in the study. Summaries of these two trials are provided in the panel pack.

The Stents in Radiation Therapy Trial is the pivotal study for the evaluation of safety and effectiveness of the Beta-cath system. Dr. Zuckerman will provide an overview of the trial design and a summary of the results.

DR. ZUCKERMAN: Good morning. My name is Bram Zuckerman. I'm a medical officer cardiologist with the Food and Drug Administration.

The START trial is the key data set for consideration of this PMA. The sponsor has previously outlined the major elements of the protocol and shown key results. The agency would like to discuss several aspects of this trial prior to presentation of the panel questions.

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The START trial was a well-designed trial. A large number of patients were randomized to beta radiation or placebo treatment. Patients, investigators, and core labs were blinded to treatment assignment.

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Inclusion criteria indicated that a patient needed a symptomatic case of in-stent restenosis with a reference vessel diameter between 2.7 and 4 millimeters. Visual estimation was performed of reference vessel diameter because this mimics real-world clinical practice. There are few sites in the United States that routinely use online quantitative coronary angiography, QCA, or intravascular ultrasound. But as expected, we saw the discrepancy between our visual reference vessel diameter results and the QCA results.

For example, the mean QCA result reported from the core lab for all vessels was 2.76 millimeters. The other point in interpretation of this trial is as noted by Ms. Peters: 95 percent of the data pertains to the 30-millimeter source train.

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Vascular brachytherapy represents a new technology for treatment of in-stent restenosis with an unclear risk/benefit profile. As such, a superiority hypothesis was chosen with a primary clinical endpoint: 8-month target vessel failure.

Target vessel failure is a conservative endpoint that includes death, non-fatal myocardial infarction, and target vessel revascularization. The angiographic and ultrasound data provided in this panel report should, therefore, be viewed as supporting data that helps to mechanistically explain the effects of vascular brachytherapy.

Next slide, please?

On this slide, we have acute results presented. You've seen much of this before presented by the sponsor. The only difference with these slides and the next two are that we will have also the 95-percent confidence interval of the differences presented.

The key point for acute results was that a respectable post-procedure percent diameter stenosis was obtained, and high rates were reported for both device success and procedure success.

Next slide, please?

There were nine cases of device failure. These cases have been individually reviewed in your panel pack report.

Next slide, please?

Please note, however, the definitions used for device failure and procedure success--I'm sorry, for device success and procedure success. Device success was defined as successful placement of the Beta-cath system, and procedure success was defined as a post-procedure percent diameter stenosis less than 50 percent without the occurrence of major adverse cardiac events during the hospitalization. Hence, such problems as initial device failure, minor device malfunction, in all cases where the bail-out box was used emergency, would not necessarily be captured in those two preceding definitions. A balanced assessment of device performance needs to include these variables and results as well as device success and procedure success results.

Next slide, please?

Eight-month safety results are shown on this slide. At 8 months there was no difference in the rates of death, myocardial infarction, stent thrombosis, site thrombosis, total occlusions, or aneurysms. Two points need to be noted.

Firstly, a minority of patients, 20 percent, were restented during this trial. The restented population may be the population at greatest risk for long-term safety problems.

The second point is that these are 8-month safety results. As previously noted and as noted by the asterisk on the bottom of the slide, there was already one stent thrombosis reported at greater than 240 days in the beta radiation arm.

Next slide, please?

Eight-month effectiveness results are reported here. The primary endpoint, target vessel failure, was reduced at 8 months by beta radiation treatment. This was a robust result. Multiple other clinical and angiographic markers of restenosis were reduced by beta radiation treatment, as noted in your panel pack and on this slide.

Next slide, please?

So, in conclusion, the primary endpoint, target vessel failure, as well as selected clinical and angiographic endpoints, were all reduced by beta radiation treatment. There was no difference at 8 months in the incidence of death, myocardial infarction, stent thrombosis or total occlusion. Device-related malfunctions were observed.

MS. PETERS: FDA would like to obtain panel input on the following questions:

The original START protocol suggested that the institutional standard of care for antiplatelet therapy after source treatment be utilized for patients who were restented or received PTCA. This regimen was modified based on recommendations from the Data Safety Monitoring Board. A report of the antiplatelet therapy usage during the START trial is provided in the addendum to the START clinical report on page 3. No incidents of stent thrombosis were reported during the START trial.

Question 1: Based on this information, please discuss your recommendations for the antiplatelet therapy for patients who receive a new stent and for patients who do not receive a new stent.

Table 31 of the START clinical report and the addendum to the START clinical report on pages 13 through 35 identify the device failures and malfunctions that occurred during this study.

Question 2: Please discuss the clinical importance of the device failure and malfunction events and the evaluation of the safety and effectiveness of the Beta-cath system.

As demonstrated by the results included in Table 1 of the START clinical report, the incidence of the primary endpoint, target vessel failure, was significantly lower at 8 months for the treatment arm compared to the placebo. The incidence of target vessel revascularization, target lesion revascularization, and major cardiac adverse events were also significantly lower over the 8-month follow-up period for the treatment arm compared to the placebo. No incidents of stent thrombosis were detected in the treatment arm, and the frequency of total occlusions was comparable between the treatment and placebo arms.

Question 3: Please discuss whether you believe the probable clinical benefit of the radiation treatment outweighs the probable risk of death, myocardial infarction, late total occlusion, and late stent thrombosis posed by the device in the intended patient population.

One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify the product's potential adverse events, and explain how the product should be used to maximize benefits and minimize adverse effects. Please address the following questions regarding the product labeling.

Question 4-A: Please comment on the indications for use section as to whether it identifies the appropriate patient population for the treatment with the device.

Question 4-B: Please comment on the contra-indications section as to whether it identifies all conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

Question 4-C: Please comment on the warnings and precautions section as to whether it identifies all potential hazards regarding device use.

Question 4-D: Please discuss whether any improvements could be made to the labeling to help minimize the occurrence of device failures and malfunctions as discussed under Question 2.

Question 4-E: Please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

Question 4-F: Does the panel have any other recommendations regarding the labeling of the device?

A summary of the physician training program has been provided in Section E of the panel pack and in the addendum to the START clinical report on pages 18 through 25.

Question 5-A: Please discuss any improvements that could be made to the training program to help minimize the occurrence of device failures and malfunctions as discussed under Question 2.

Question 5-B: Please identify any other important elements that should be contained in a physicians' training program for this device.

The panel pack includes the available one-year data from the START trial, the available one- to four-year data from the BERT feasibility trial, and the available data from the BRE European trial.

Question 6: Based on the clinical data provided in the panel pack, do you believe that additional clinical follow-up data or post-market studies are necessary to evaluate the chronic effects of intravascular radiation administration? If so, how long should patients be followed, and what endpoints and adverse events should be measured?

This concludes the FDA's summary presentation.

ACTING CHAIRPERSON TRACY: Thank you.

At this point we'll move to the open committee discussion, and I'd like to ask Dr. Simmons to begin the discussion with his review, and we'll go around the table after that. And I'd just remind the panel members to restate their names and speak into the microphone when they're asking their questions or making their comments.

Dr. Simmons?

DR. SIMMONS: Thanks. Well, it's a very nice presentation by the sponsor and the FDA. I have a few questions.

The data that the sponsor presented I think presented a better clinical outcome than the data that's in the panel pack or that the FDA presented. I mean, the 8-month stent segment restenosis rate was 14 percent versus 14 percent, which is a 27-percent reduction. However, the target lesion revascularization at 240 days was 86 versus 76, and you were presenting 31 percent. So it's actually about a 9- to 10-percent reduction in total vessel failure at the 8 months--is that right?--as opposed to the 30 percent that I saw on your slides? There's quite a difference between 30 percent versus 9 percent.

DR. BAILEY: Is it possible he's talking about a relative reduction?

DR. SIMMONS: That's what I'm interested to see.

DR. POPMA: I wonder if we could just go back to our slides and the presentation just very briefly, if that will help find out where the discrepancies are.

I should also note that it is difficult to take numbers out of the event-free survival curves and then put them back into the rates that are measured. The 240 days is absolutely accurate, but some of the data that's in the pack is extended out further than that and before that. So I want to make sure of the 240-day endpoint for event-free survival curves.

Let's go back and discuss those. If you can put up, Richard, just the graph that has the four reductions of TVF, MACE, TVR, and TLR, the one slide with four graphs.

ACTING CHAIRPERSON TRACY: Could you also introduce yourself for the--

DR. POPMA: Sorry. I'm Jeffrey Popma.

Now, we can go by these one by one, if you like. I think that these absolute rates have been relatively consistent and should be consistent to the rates that are reported in the panel pack.

DR. SIMMONS: Well, they're not, actually. Why don't you go to page--let's just get on the same page here. Go to your panel pack, page 414, and you've got TVR-free at 240 days, 81.4 percent in the treated group versus 72 percent in the placebo group, so the difference is only 9 percent.

DR. POPMA: I got it. I'm going to defer to Rick Kuntz, who did the statistical analysis for this.

DR. SIMMONS: And that's different than 32 percent.

DR. KUNTZ: The numbers that you're referring to is the absolute difference. This is a relative difference.

If you look here, the difference in TVF there is 26 minus 18, which is 8 percent. And then you're seeing a difference in the MACE-free or TVF-free of 9 percent, which is consistent with the differences between sensoring and non-sensoring survival analysis versus a discrete analysis. Maybe--Dr. Bailey, do you understand what I'm talking about there?

DR. BAILEY: In other words, 9 percent is 31 percent of 26.

DR. KUNTZ: Right. So the difference of 9 percent in the TVF and 8 percent in the event-free survival or vice versa is pretty typical when you're using a sensored analysis for survival versus one that is a discrete analysis at 240 days. To me that's pretty clear. I'm not quite sure--so 31 percent refers to the relative difference you see here, but the 9 percent you're referring to is the absolute difference. The absolute difference here is 8 percent as well.

DR. SIMMONS: Okay. So what we're actually talking about is an 8-percent improvement clinically.

DR. KUNTZ: Right.

DR. SIMMONS: A 9-percent improvement clinically.

DR. KUNTZ: Right. Again, if we refer to the MACE or the TVF here, the absolute differences there are in the 8 to 9 percent range.

DR. SIMMONS: Okay.

DR. KUNTZ: Which is similar to the event-free survival we're seeing there.

DR. SIMMONS: All right. You know, I understand that most of the device failures did not result in any complications to the patient and any real damage. But, you know, the physicians doing your clinical trials, they're more skilled physicians. They've got more back-up. They've got more interest in what's going on. But we're still talking, I think, a fairly amazing, almost 20-percent incidence of some device failure, either minor or major. And even though it didn't appear to have any clinical impact in the physicians that were performing the study, I'm just wondering what happens when physicians who do two angioplasties a month and don't have any company representative around, whether that's really going to translate into no complications to the patient.

In addition, if we look at page 221, where Dr. Zuckerman analyzed the differences between your number three and your number four revision, the incidence of drift and everything else didn't really seem to be affected by putting the lights on the box and changing your connector.

So I'm just wondering if one of the clinicians might address this issue, my concerns.

DR. SPEISER: Burton Speiser, radiation

oncologist. I think the primary problem with both the drift and the transit time is the lack of observation of the observer. It's a very simple process, either by feel before the LED lights were added, or by watching the LED lights. The primary problem is the training of the individuals such that they pay attention to that, and I don't want to put down my colleagues too much, but it isn't a very hard job really to keep the pressure in there.

Part of the training process is to use the device and ensure that they know how to keep the pressure constant, which is, in effect, a very easy process.

DR. SIMMONS: I don't know. I mean, these are very motivated, highly skilled people. If they can't do it, do you really expect people in other cath labs who aren't as motivated to be able to do it?

DR. SPEISER: I think the problem is primarily with the radiation oncologist who is in the cath lab for the first time, feels in a foreign territory, and I think what is necessary is the feeling that they're comfortable there and they know how to use the device. And that will take training. Most radiation oncologists probably have never stepped into a cath lab before, and I think that's why the training and doing the mock procedures is quite important to make sure that each radiation oncologist feels comfortable.

If you play with the device, you'll be surprised how simple it really is, so that I do have a little difficulty trying to explain a 20-percent rate of transit problems and drift, when, in fact, if you use the device in a mock session, it's very easy to send the sources out and keep them in station or in place.

Now, I know that may not be answering the question, but I do have difficulty in understanding why many of my colleagues had difficulty with it.

MR. GREEN: I'd just like to also add to that that the trial did actually include 50 centers, and we believe that was--we tried at least to develop that trial with those centers so that we included both, if you will, the normal usual suspects or the normal usual trial centers that would be seen in these type of trials so we had that component of an understanding of clinical trials, as well as the regional and, if you will, everyday hospitals that would use such a system.

We did learn that if you look in your panel pack at the section on the device observations, for instance, with regard to what we call the manual removal procedure or what we term there the bail-out procedure, that as time went on and as enrollment went up, there was a decrease in the rate of the use of that procedure. So, therefore, as people became accustomed to the cath labs, people became--we had improved training from experiences in the trial, we were able to modify not only the device but the user's understanding of the procedure and how they could apply that device and that procedure to obtain the results that we found in the trial.

DR. POPMA: If I could just maybe help this a little bit with just a clinical perspective, as the cardiologist, of course, we're not responsible for moving the radiation source, but we actually do have a lot of experience with catheters. And some of the issues with respect to the transit time may well have related to very simple things like having the touie borst (ph) too tightly ratcheted down so that they couldn't move back and forth.

We learned these things as we went through, and I can tell you the procedure that I performed today is very different than the procedure that I performed a year ago because I have much more attention to having the touie borst open, it's loose, the catheter being straight, and helping the radiation oncologist deliver the sources more quickly, as well as the fact that we stay on fluoro a lot more to make sure that there's no source drift.

All of this is covered in training, and I think it's very important to emphasize that a lot of the things that you're discussing in 20 percent, none of us would want to have that shown prospectively. But they are covered in training, and I do think that we all need--we've all learned from this, and I think that we perform a very much better procedure now than we did before. We just have to, you know, show that, I think, with data.

DR. SIMMONS: So even though the radiation oncologist delivers the seeds, the cardiologist should be able to see whether this thing is drifting or not, right?

DR. POPMA: Absolutely. And we will do--we do that and have done that, and we're very much aware of that now, by stepping frequently on the fluoro pedal. There's nothing that prevents the--

DR. SIMMONS: Well, there is something in the manual about how many times, how often it should be observed, and--

DR. POPMA: Exactly.

DR. SIMMONS: Do you know what those are?

DR. POPMA: Well, right now we--you know, as I say our clinical perspective is--I'll let Drew address what the IFU is, but we do that very, very frequently now in the catheterization lab with a much more heightened awareness about the importance of drift. And by doing that, we actually can catch events. But I'll let Drew--Dr. Green discuss what's in the IFU.

MR. GREEN: During the clinical procedure, the protocol described using fluoroscopy, I believe, every 10 to 15 seconds to observe to see position and location of the source train and correct--the instructions for use included in your panel pack also reflect that.

One thing I would like to also point out is that we did--you know, when we went and designed a clinical trial, we didn't have some of the experience, of course, you go to gain from a clinical trial. So we applied what we believed to be conservative estimates based on bench testing, which, as you know, when you go into a clinical trial is your first available information. We prospectively defined what we believed would be some measures we would want to look at, things like source drift, source transit times, et cetera.

The panel pack does now describe its modifications to the instructions for use reflecting source transit, for instance, which also goes into the train. Instead of just having recommendations based on the bench testing, we have recommendations that are based on really three things: one, the bench testing that was conducted over the expected possible pressure ranges by different users; two, experience from the START trial, what was actually reported in terms of time to send or return of source train. If you look in the panel pack there, I think you'll find that the actual--when it was reported, it was reported between 5 and 14 seconds. And then, third, we went to our oncologists and our medical physicists that participated in the trial, and we asked them what would be clinically acceptable based on what the device can do and what is necessary to occur during a clinical procedure. And we put all these things together, and we have a recommendation, which is in the panel pack, instructions for use for 15 seconds for source transit. If you don't see the sources arrive where they're expected to arrive within 15 seconds, you should then perform your manual removal procedure, which I think, again, as we pointed out just a minute ago, as time goes by, as enrollment goes up, as people become more familiar with the system, that is on the decline, indicating that the additional training and the experience they gain in the cath lab as a team--because it is a team approach--is beneficial in changing that.

DR. SIMMONS: You know, I've got some questions about the training program, which is actually very much at the end of the thing. Should we--I mean, because I think this addresses part of this problem, but maybe we could put that at the end and I'll just keep going with the clinical stuff now. Okay?

ACTING CHAIRPERSON TRACY: Okay.

DR. SIMMONS: All right. On page 413 of the submission here, it's interesting--and I think you brought this up--that only 69 out of your 476 patients had--which is 15 percent--got 60 to 90 days of antiplatelet therapy, and only 13 of 476 patients, 2.7 percent, got anywhere near 90 days of antiplatelet therapy. And yet your recommendations in the labeling are going to be for greater than 90 days of antiplatelet therapy.

I mean, I realize that a lot of cardiologists would want their patients on antiplatelet therapy for maybe other reasons. A lot of us keep them on them anyway. But, I mean, is it really necessary that we put in the labeling--I mean, you didn't do it, and you didn't have a problem. So where did the 90 days come from?

MR. GREEN: As Dr. Popma presented in his presentation earlier, initially at the beginning of the trial, the initiation of the trial, we had the recommendation for physician discretion. As the trial went on, we had information from the Data Safety Monitoring Board, from the Beta-cath system trial, a *de novo* and restenotic lesion trial that suggested that it may be beneficial to patients to have extended antiplatelet therapy if they receive a new stent. And the recommendation was made by them and submitted to the FDA and the IEE to make that change to the protocol, minimum 90 days antiplatelet therapy for patients receiving a new stent.

Therefore, at the end of the trial, we carried that recommendation over into our labeling because it did define, if you will, the experience that we attempted or we implemented to investigate in the trial, and it was a recommendation of the trial. So it's approved protocol and we carried it over.

Dr. Benot (ph) is our medical director at Novoste Corporation and an interventional cardiologist at Montreal Heart Institute, and I think he'd like to add something about antiplatelet therapy.

DR. BENOT: I think, as was presented either by us or by the FDA, the data that we have concern that type of antiplatelet therapy, that type of adjunct antiplatelet therapy. We have not studied anything else. Why we have the movement from one type of antiplatelet therapy was left to the discretion of the physician at the beginning, because when we start that study in September '98, we don't know, we have not the knowledge of any event related to late stent thrombosis and radiation.

At this time we have already the Beta-cath trial in process, which is a different indication, is a treatment of *de novo* lesion with better radiation. This trial, the Beta-cath trial, has two arms: a PTCA arm, a balloon-only arm, and a stent arm. In the stent arm, we finally find out by the end of October '98--the DSM Committee chaired by Tom Ryan come to us and report some of the complications related to the late stent thrombosis. At this time we started to apply longer adjunct antiplatelet therapy, and at this time we propose two months. By March '99 we were secure, we are sure that the problem was still there, and at this time was implemented the minimum of three months of adjunct antiplatelet therapy.

That's the detail we have from the Beta-cath trial. We have never had a problem as reported in the START trial for that as medical officials, and we discussed that, we translate the data we learn from *de novo* stent and radiation to in-stent restenosis and radiation and apply to ask our investigator to prescribe a minimum of three months when they implant a new stent.

DR. SIMMONS: It's just it's interesting that you didn't have any problems in this study and only 2.7 percent of your patients had, you know, anything close to ninety--but I guess there's no harm in putting--

DR. BENOT: As the data that we have--and I can have the report from the statistician from the Beta-cath trial, Stuart Pocock, we put on the letter from Dr. Stuart Pocock, and on the Beta-cath system trial, again, different education, *de novo* lesion, but using a stent as the arm differentiating with the balloon-only. And based on the analysis and listing of the current interim data, the incidence rate of late stent thrombosis, Q wave and non-Q wave MI are all satisfactorily much lower in the patient first randomized and treated in the provisional stent branch following the protocol amendment, which is a minimum of 90 days of adjunct antiplatelet therapy (?) .

These findings are based on 492 patients randomized in the provisional stent branch before the protocol amendment with a median(?) follow-up of 18 months, and, further, 449 patients randomized in the provisional stent branch after the protocol amendment, which is the minimum 3 months of antiplatelet therapy, and that with a median follow-up of 9 months. That's the detail we have. We have no other data than that to explain why the level of the protocol of adjunct antiplatelet therapy.

DR. POPMA: I appreciate your letting my colleagues address the background behind that, but as the principal investigator of the trial, I'm comfortable with the statement of at least 90 days, because we do feel that we only had 50 patients in the study who received new stents and radiation therapy, approximately. So to make a definitive statement that there were no subacute stent thrombosis within the first 242 days, there may be some broad confidence intervals to that statement. In addition, we do have this patient at 244 days that had an episode that could be very consistent with a subacute thrombosis event.

So I think I am comfortable for those reasons in saying a minimum of 90 days of antiplatelet therapy.

DR. SIMMONS: Now that you are up there--

[Laughter.]

DR. SIMMONS: So the new stents were discouraged.

DR. POPMA: That's correct.

DR. SIMMONS: But 20-some percent got new stents.

DR. POPMA: I think that's a good point. Let me just again walk through very simplistically exactly how you got into the study and how you got a new stent.

First of all, in order to be randomized in the trial, one had to have a successful result. You had to have a 30 percent or lower residual stenosis. So the concept was that in order for you to make the decision for randomization, you didn't want to have a new stent in place. At least we didn't have a new stent in place. So the radiation was then delivered. And time passes during that period of time, and we know some things about stent restenosis.

One of the things we've learned from work done at the Washington Hospital Center, Roxanna Mayron and Gary Mintz, is that there is an early recoil that sometimes occurs. The mechanism of treatment for in-stent restenosis, you extrude the tissue outside the stent struts, and then within the first 30 minutes or 40 minutes, there's actually a collapse of that and the tissue comes back within the stent. And there's time that passes as we're delivering the radiation effect.

So it's understandable that in some patients the residual stenosis would look a little higher after a time delay than it would be if you just ended the procedure and we called it a successful result.

So the new stents that went in went in for two reasons: one was there was a dissection that had to be treated; or, secondly, because there was a residual stenosis that was within the lumen.

DR. SIMMONS: Well, wasn't a dissection a contra-indication to giving the radiation therapy in the protocol?

DR. POPMA: Yes, that's correct. In order to get into the procedure, one had to have a successful result, which was the absence of dissections. But then, as I say, there is a dynamic change that can occur within the lumen. Sometimes the recoil that occurs from re-extrusion of stent plaque into the vessel wall looks like a dissection. It's a flap that can fall back in. Angiographically it's somewhat difficult to tell those. But what we did is we really lowered what was a prevailing rate of 80 percent new stent use for in-stent restenosis down to 20 percent. And if the truth be known, what we know about the START data now, we'd like to get that even lower. And so some of the things that we would really like to say with this study is that we really want to reserve the use of new stents in the study for bail-out circumstances, some circumstance that happens during the procedure that, after radiation therapy, one has to treat with a stent. That can be a new lesion at a new site or within the site that you're treating initially.

DR. SIMMONS: So you would say that these mostly were done--the new stents were put in after the radiation was already given?

DR. POPMA: That's correct.

DR. SIMMONS: Or where the placebo was given.

DR. POPMA: They all were, yes.

DR. SIMMONS: And so did--I mean, I guess it could significantly affect the results. Did you look and see were they equally divided on both sides for stents, for the placebo versus the active--

DR. POPMA: There was no deleterious effect of radiation on causing more stent in group than another group.

DR. SIMMONS: But did one group have more stents than the other group?

DR. POPMA: No. They were equally balanced between the two.

DR. SIMMONS: How about the breakdown on the diabetic patients? I was especially curious. Did you look at that as far as--

DR. POPMA: Diabetic subset? I'm going to let my colleague, Dr. Kuntz, address the subset for diabetes.

DR. KUNTZ: Diabetics were evenly distributed, and there was no effect of diabetes on the instance of restenosis in the trial.

DR. SIMMONS: Okay. So there was no beneficial effect either.

DR. KUNTZ: There was no differential effect. Both groups benefited. It just was no differential effect. That is, the interaction between diabetes and radiation therapy was not positive.

DR. SIMMONS: Okay. You know, I guess I'm just going to ask the radiation oncologist--this is exposing my naivete here, I guess, but I just have to ask this. I guess I'm a pessimist by nature and a therapeutic nihilist to a certain extent, and I guess I just don't believe that you can put radiation inside a coronary artery and have a beneficial effect without also having a risk of a negative effect. I mean, there's got to be some downside to this as far as creating aneurysms or scar carcinomas or something. There has got to be a downside.

I guess I just want your opinion. You know, what's the downside and how long do we have to wait until we see it?

DR. SPEISER: Probably the easiest to dispel is the incidence of cancer from this as an overall problem. About one-tenth of a percent of the total dose is delivered from the Strontium, so that by itself is very insignificant compared to the fluoroscopic dose, which would be a greater concern. The only concern I would have is that it's a very high point dose, so it would be more likely to be a concern as far as increasing fibrosis or aneurysmal formation.

At the present time, the data that we do have is the BERT trial that shows neither of those two effects have increased. So the answer is that with the available data, which is very scant, there has not been a late deleterious effect. However, I think most radiation oncologists would agree, because radiation effects are delayed, that we would like to continue looking for it for a longer period of time.

DR. SIMMONS: What are talking here? I know some radiation effects, like for lymphomas, can even occur ten years later. Are we looking at something that may all of a sudden show up five or ten years from now with severe scarring in that area?

DR. SPEISER: Most late effects, such as scarring or vascular effects, usually occur between 6 and 24 months after completion of radiation. So that I would expect that most of them will show up in that time period. The later effects, as you mentioned, for instance, carcinogenesis, is delayed. Lymphomas are the earliest cancers, about 10 to 20 years. Sarcoma is 20 to 30. So that for those we'd have to wait a much longer time. However, I'm not, as a radiation oncologist, concerned about the carcinogenesis, but just the direct immediate effects of the high dose on the vessel wall, and that I anticipate that we should see for the most part between 6 and 24 months from the completion of the procedure.

DR. SIMMONS: Okay. Maybe our radiation people will have something more to comment on that. Just one more and then I'll--

MR. GREEN: Perhaps, if you'd like, we could have maybe one more opinion from one of our radiation oncologist?

DR. SIMMONS: Maybe not. Maybe we'll let our radiation oncologist ask some more questions on that issue since I'm not...

As far as your warnings and your contraindications section on your labeling, this study actually did eliminate people with ejection fractions less than 30 percent and it did eliminate people with myocardial infarctions within the last 72 hours. Shouldn't those be--I mean, since those patients weren't studied, I just want to know shouldn't we put some warning or at least some contraindication. I'd like to have your opinion before we discuss it when you're not available to comment.

MR. GREEN: When we developed the protocol and we put it together to study this trial, as you do in many trials, there are a lot of things that you put in the trial to try to either limit bias or try to determine what the effect on the patient was. For instance, the one recommendation in the protocol you talked about was myocardial infarction within 72 hours, and that was to be able to delineate the baseline factors for a patient.

We are recommending that the patients--the instructions for use reflect what we did in the clinical trial. However, like I said, they were recommendations in the--or exclusion criteria in the protocol that were specifically limited to the ability to evaluate the patients in the follow-up to see if the therapy was effective.

DR. SIMMONS: I think that's fine, but for right now what I'd have to say is at least when go to discuss this later on, I would have to say those are things that would have to be added, at least a warning if not a contra-indication, if they aren't there now.

DR. POPMA: Respectfully, I'm not a labeling expert, but as a clinician, I don't see that there's any reason to suspect that in a patient who has recurrent refractory in-stent restenosis and ejection fraction plus the 30 percent that this therapy should be contraindicated. And I'd only hope that the trial design construct could be described in the labeling, and then a very careful construction of what was done in the trial and the inclusion sets. But I think at this point in time, I would say from a clinical perspective that I wouldn't know that there'd be data suggesting it should be contraindicated in a patient with an ejection fraction plus the 30 percent.

DR. SIMMONS: I've got some other issues on the training session, but maybe we can put those off until everybody else has had a chance.

ACTING CHAIRPERSON TRACY: Okay. I'd like to ask our statistician if he has any particular questions, and then we'll go--we'll probably break for lunch before we go around the rest, but if we could have Dr. Bailey ask any questions.

DR. BAILEY: Why don't I just list a few questions? Because I tend to get confused when I hear the answers to them.

So, in no particular order, well, first of all, I'd like to echo I thought this was a nice study and well reported.

With respect to the analysis of these minor--what are they called?--MDMs. That's all I can remember. Device malfunctions. I notice that there was an analysis of the clinical impact, and this probably will just reveal my ignorance. I noted that you pooled the drift and the long transit time. And I was wondering if that's based on a *priori* considerations that those would have the same impact or just--I would have thought, I guess naively, that drift would be a relatively more important issue and perhaps should be analyzed separately. And in that same vein, if you're trying to understand the impact, it would be useful to look at the edge effect with respect to those cases that had drift. I thought that was a nice analysis of the edge effect where you had lots of power for quantitative analysis. That's sort of one set of questions.

The second one, actually sort of related: Did you actually look at the cases with these malfunctions to see if there were any patient differences? In hearing the discussion, it sounds like this is more or less a random occurrence, but I didn't know whether you looked at whether there were patient differences in those that had the drift problem.

Relative to the recommendation of length of antiplatelet therapy, do these results in the START trial, are they consistent with the earlier--the Beta-cath results? In other words--I'm sort of following up on your comment. If you looked at the results, there's a certain number of patients that did not get what would have been considered the desirable length of antiplatelet therapy and, nevertheless, no events, no thrombosis occurred. And I wondered if it's just too small a sample or if those results could be compared to the earlier results and see if there's anything different about these data. That's question two.

The third question has to do with the--I think I saw among the analyses that were in the packet that wasn't presented some modeling done of the effect of lesion length and treatment and an interaction term, which I thought was very interesting and showed that the treatment effect was more pronounced at longer lesion lengths. And I guess I would just ask if this has something to say about the risk/benefit ratio in terms of the labeling aspects, and I thought that analysis should be made more accessible to the user to determine if there's a lesion length that's less than optimal.

And then my last question has to do with the heterogeneity between sites, and I saw some analyses in the packet, but I didn't really understand what was being done. And in particular, were analyses done to suggest that sites had different overall restenosis rates, or was there also differences in efficacy rates? So I guess it was more just ignorance that I didn't know what was being presented.

ACTING CHAIRPERSON TRACY: I'm not sure how you want to approach that. Maybe one question at a time? You can identify which aspect you're dealing with and also identify yourselves.

DR. KUNTZ: Rick Kuntz. I'm a cardiologist and a part-time statistician, I guess, although I'm a little intimidated by Dr. Bailey.

Why don't we just start from the top there?

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DR. BAILEY: Drift and--pooling drift and transit time.

DR. KUNTZ: Right. We had a variety of different MDMs. There were four. There was the drift, transit time issues, inability to deliver the catheter, and some other issues that were like one person per category. They represented a variety of different fields that were prospectively collected in the case report form, all classified as potential device malfunctions.

In looking at that overall data set, in order to reduce multiplicity and try to deal with, you know, diminishing the alpha to zero, we focused just on the radiation issues. So the decision to pool transit time and drift was an issue of power and reduction of multiplicity. So we haven't looked at the individual events themselves because they were evenly distributed. I think there were something like 80 cases overall between the two groups that were MDMs, and there were about 40 and 40 on each one, drift versus that. So my expectation is that since we generally found no difference in the adverse events with the pooled group that we probably would be completely underpowered to look at the individual groups themselves, and it probably wasn't worth the analysis.

DR. BAILEY: What I was thinking, though, is if you looked at the edge effect in a very quantitative way,

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looking at the delta minimum luminal diameter in that region and separated specifically the drift ones, you might have some power to look at it.

DR. KUNTZ: Right. Your second part of the question about did we look at drift effect with the edge analysis specifically, we have not done that, and I agree that would be an interesting analysis because we may have enough power there because they're both continuous measures. And I think that would be an interesting analysis to do.

DR. BAILEY: Patient differences in terms of predicting who--was that just a random event?

DR. KUNTZ: Yeah, we spent--the question was could we look at--were there any anatomical patient factors that explained patients who had these MDMs. So we spent a lot of time looking at those factors, and we couldn't find, that is, by generally exploratory analysis, that there were any indicators of increased tortuosity, that there were indicators of the distribution of the vessels. For example, was a right coronary artery more likely to drift than a left coronary artery? The amount of calcium that was in the vessel, the age of the patient, I think a variety of different things. I'm thinking off the top of my head. We tried to evaluate whether we could predict who was going to have a drift of source, and we couldn't find them.

Practically speaking, the issues of drift to start with and the intransitude to some degree were really issues of the radiation oncologist, an issue about the touie--the hemostatic device more than they were issues of patient factors; that is, the device itself is designed not to have any kinks and is bulky enough that it generally won't be delivered down very, very tortuous vessels to allow the catheter itself to impede delivery. So delivery impedance were issues of maintaining pressure and issues of the hemostatic valve. So we think that those were the things that explained the differences, not issues of patient characteristics, where we can say that this patient is at more risk of a drift than the other patient on initial exploratory analysis. We couldn't identify patient factors.

DR. BAILEY: Can you compare the thrombosis rates between patients who in the START trial had new stents placed and did not get 90 days of therapy to the earlier data that were the basis for--

DR. KUNTZ: In the Beta-cath trial, we're looking at a 1,500-patient trial compared to a 476-patient trial, the START trial. So the history which was reviewed is important to understand.

In that trial, patients were treated initially with balloon angioplasty. Then depending on the result, the physician decided whether they would go down a PTCA branch based on a very, very good result for which the patient was randomized to placebo versus active therapy blinded with no further stent placement, or if the result from balloon angioplasty was suboptimal, they were arbitrarily decided to go down a stent branch and then randomize after that.

So we had a fairly large volume of patients initially, as you can imagine, because of the stent interest at that time of patients who had new stents placed, on the order of five or six hundred patients, as opposed to 50 patients with new stents in this study. So the opportunity to observe stent thrombosis was greater in the Beta-cath trial than the opportunity to observe stent thrombosis in this trial.

So, initially and early on, when the Data Safety Monitoring Committee with its blinded review of the data identified that there were some problems going on when new stents were placed and patients exposed to radiation therapy and expected--and declared that they wanted to extend antiplatelet therapy--this, by the way, was reviewed with the FDA and the protocol was changed. We anticipated that this also might be an issue in the START trial where new stents were placed.

However, at the end of the START trial, the 476-patient trial, only 50 patients received a new stent. So we are extrapolating the potential for stent thrombosis, even though we had excellent results in this study, to our experience with over 500 patients early on where there was a higher incidence of stent thrombosis; hence, the interest in potentially having 90 days or more of antiplatelet therapy.

DR. BAILEY: The interaction between lesion length and treatment effect.

DR. KUNTZ: It's very interesting interaction. We mainly saw it in the restenosis defined by the analysis segment, not by the stent segment. And what we see is that, in general, lesion lengths are associated with a higher risk of restenosis. That's been true with multiple data sets, especially in non-radiation areas. That is, patients who have longer lesions tend to have a higher risk of restenosis than patients with shorter lesions.

When we look at the analysis segment, which actually lets us have the opportunity of measuring the minimum lumen over a wide area, we start to see that radiation therapy had an extra effect on patients with longer lesions, and that made sense; that basically the increased risk the patient was exposed to with a longer lesion afforded a more profound treatment effect from radiation therapy than those who had shorter lesions. So the interaction term of longer lesion lengths and radiation therapy made sense to us, understanding the underlying risk the patient had with longer lesions.

DR. BAILEY: In fact, based on the coefficients, if you have a lesion length of 8 millimeters, you're at dead even.

DR. KUNTZ: Well, right. It's hard to go back and say where the breakpoint is of radiation therapy being ineffective at some level. All we can say is that the continuum shows that longer lesions have more potential for effect than shorter lesions. But these lesions have been linearized in a linear model. We didn't do a lot of non-linear models to see where the breakpoint is. And so I think that it's an interesting extrapolation, maybe the basis of a hypothesis for a new study.

DR. BAILEY: I agree it's not very exact, but I think it points to at least an issue if you're a user whether you want to embark on radiation therapy in a shorter lesion.

DR. KUNTZ: That's a good point.

DR. BAILEY: And, finally, the site heterogeneity.

DR. KUNTZ: Right. The site heterogeneity we thought was typical in most of the studies, that is, the overall distribution of treatment effects for a 50-patient trial showed--a majority of patients showed a similar result as the mean effect overall. A couple sites out of the 50 had the opposite results, which you typically see in a normally distributed trial.

The other heterogeneity issue dealt with--there was one or two sites that tended to use new stents more often than others per se. However, in the overall analysis, the restenosis rates didn't differ, so we didn't see a profound effect on the site.

We performed the typical boilerplate pooling analysis for the FDA looking for interactions between treatment site and the overall main effect, and albeit that's another powered analysis usually, we didn't see any deviation from the normal studies that we saw.

DR. BAILEY: Thank you.

ACTING CHAIRPERSON TRACY: Okay. At this point I think we'll break for lunch, and if we could resume at 1:15. And I would like to remind the panel members not to discuss the contents of this meeting.

[Luncheon recess.]

AFTERNOON SESSION

[1:30 p.m.]

ACTING CHAIRPERSON TRACY: We'll resume the open committee discussion, and we'll resume with the panel questions, and I think we'll start down at that end, please. Again, just to remind everybody to identify yourself and to speak into the microphones.

DR. AYERS: Okay. I moved up a little in the order, but I have a couple of questions. One, your presentation indicated that you were giving 18.4 Gray and 23 Gray, depending on the vessel size, but actually since this is non-centered sources, an asymmetric lumen, shadowing by guide wire and stent, what really was the dose range for these studies, minimum, maximum, your estimates to the (?) .

MR. GREEN: I think we'll let Dr. Crocker, radiation oncologist and investigator in some of the BERT feasibility studies and who helped in the START trials, answer this question.

DR. CROCKER: My name is Ian Crocker. I'm a radiation oncologist at Emory University. I'm a consultant and a shareholder in Novoste, and, in addition, Novoste has licensed intellectual property from Emory University, and I am co-owner of that intellectual property.

Within the vessel wall, there is a wide range of doses that are delivered, and that's really true of any brachytherapy source. We did prescribe a dose at 2 millimeters from the center of the source, and that initial prescription represented a small incremental increase in dose over what was prescribed in the Beta Energy Restenosis Trial based on anticipated shadowing of the source by the stent struts.

We had done some measurements which had shown that there was approximately a 10-percent decrement in dose immediately underneath the stent struts, and as a result of that, we recommended increasing the dose that was delivered in the START trial by 2 Gray, which represented an 11- to 14-percent increase in dose over what was delivered in the original BERT trial.

DR. AYERS: Do you know how much effect the dose varied from the fact you had a 6-millimeter variation in vessel size for the same dose, so I guess that would be 0 to 3 millimeters in variation from the vessel wall to the prescription point, and also the fact that it wasn't centered.

DR. CROCKER: Right. With the cohort of patients who were treated in this trial, we undertook a retrospective analysis of dosing using intravascular ultrasound images, and information on that has been submitted to the FDA as part of this submission.

Basically, the catheter assumes a relatively centered position within the lumen based on these IVUS ultrasound images, and really there are only minor differences in the doses, you know, that are received to the vessel wall with active centering of the catheter within the lumen compared to non-centering of the catheter.

DR. AYERS: One other one, I guess just for clarification. It wasn't clear to me. When you added new stents to about--what, 20 percent of the patient population, as I recall.

DR. CROCKER: Correct.

DR. AYERS: Was that done before or after the radiation therapy or a mixture?

DR. CROCKER: Those new stents were added after the radiation therapy was delivered, so that the protocol specifically excluded patients with stent sandwiches or stent within a stent, so that we didn't anticipate that there would be any areas in which there would be stent overlap and more than approximately a 10-percent decrement in dose due to the shadowing effect.

You know, I should say that that decrement in dose becomes less important as you get further away from the stent. In other words, there's a relative filling-in of dose at increasing depths beneath the stent.

DR. AYERS: Okay. One other thing I noticed, you spent a lot of time on indicating how small the dose to the patient was from--or incremental dose to the patients from the beta therapy, particularly whole-body, which is certainly true. But nowhere in there I saw addressed is how much increase in the dose was due to the fairly substantial additional fluoroscopy in sign, particularly, you know, monitoring the source position every 30 seconds. Do you have any value for the added skin dose for that additional fluoro?

DR. CROCKER: I'm not sure that I have any additional information regarding the fluoroscopic dose. Maybe Dr. Popma might want to comment on this.

DR. POPMA: These are very short pops of fluoroscopy and not a long length. You really just have a second or less, just to check the position of it, which you can review on your video replay.

DR. AYERS: Okay. But every 15 seconds, that would be, what, over a 2-minute treatment time?

DR. POPMA: Again, just a second or so each time.

DR. AYERS: And I was curious--and the last item I have for right now. I guess I forgot--I'm Robert Ayers, NRC. I didn't identify myself starting this. Novoste introduced later in the study, when problems were uncovered and we investigated some of these and, in fact, generated an information notice on source transport difficulties, particularly through the introducer or touie borst valve or whatever was used for that. It's known that if that's overtightened, it can block the sources going either in or out, and I think well less recognized perhaps by the panel, if you overtighten it too far and go past the elastic limits of the catheter, that blockage stays there even if you loosen the valve. And they introduced this introducer sheath as a corrective measure for that but don't require it, and I wonder how come.

Our experience has been that the cardiologists don't use it because it's an extra step, in the one incident we looked at.

DR. POPMA: Drew?

MR. GREEN: What we found when we--first, of course, you're correct. We did qualify an arrow sheath introducer as an additional accessory that the clinician could use in the procedure. They would place the catheter through the introducer sheath, which is its labeled indication for use for introduction of percutaneous catheters. And, therefore, when they would tighten the touie borst, the hemostasis valve down onto that sheath, it would protect the catheter.

What was found in talking with the centers and looking at what was happening, especially the center that you were talking about, was that this had, if you will, a learning--it was part of a learning curve, you know, part of the learning of using the device, and that the interventional cardiologist places the catheter and, you know, it's their job every day to maintain placement of that catheter, angioplasty catheter, guide catheter, what have you. And so that's their job.

So now they have a new player, a new team member who's also involved with the interaction of that catheter with the transfer device. So it's part of the training, you know, of the team working together, about moving and then learning when to tighten and how much to tighten on the catheter to allow for passage of the source and, you know, to compensate for another person being in the team.

So they wanted the ability to have this as a tool if it was necessary to use in their practice, and if not, or if they felt that they were at--or had demonstrated they were at the learning curve to where they didn't need this tool, they didn't have to use it. And this becomes very important because in the training section of the panel pack, we actually talk about, you know, going through experiences from the trial or all the trials and evaluating what the proper--you know, how a user would use the system. And as part of the hands-on training and the mock training and these pieces of the training, it's important for the clinicians to determine, you know, of the optional accessories such as the arrow sheath and the fluid management system, how they would apply that in their practice; in other words, what works best for them so that they can use this system the most effectively to gain the results that were seen in the START trial.

DR. SPEISER: At our institution, the radiation oncologist uses the arrow flex sheath, will flush it and place it over the delivery catheter so that there is no time delay for the cardiologist. And it is my intent in the training program to train the radiation oncologist to do this and to use it all the time, unless the cardiologist specifically says they do not want to use it.

DR. AYERS: Well, we're strongly considering making that a mandatory requirement. That's why I wanted to ask the question, at least at our regulatory agency.

And one last one was with our upcoming change to our medical regulations--and I'm assuming--I'm not saying that that's, in fact, the way it will work out, but most cases for brachytherapy and particularly high dose rate, we have a mandatory requirement coming now that the licensee, user, medical physicist, you know, the medical institution, however you want to characterize it, is solely responsible for the calibration of the brachytherapy source dose rate. And going over your submission, particularly in Section 2, it is not clear to me that you provide the tools with your system to allow the medical physicist at your customer site to perform proper dose rate calibrations on these sources.

MR. GREEN: We understand that some sites do at this time have requirements at a site level, possibly there will be other requirements later for site verification of dose rate, et cetera. And we do have proposals on how to handle that. And I think that Dr. John Lobdel, our Director of Radiation Management, can speak to that and let you--you know, what the proposals we are planning to do at the sites to be able to address that are.

DR. LOBDEL: John Lobdel, employee of Novoste. We have a source train that was calibrated at NIST to determine the dose rate at a half millimeter--I'm sorry, at 2 millimeters inside the--in water--I'm sorry. Let me go back. We have a source train that was calibrated by NIST to measure the dose rate at 2 millimeters from the center line of the source train in water. This train is our transfer standard. This train is used to calibrate all the trains we send to the clinical sites.

Now, during the clinical trials, we had two sites that asked to verify our dose rate. We worked with them on this. The tool we have is a solid water block that positions the center line of the source train at 2 millimeters from a film plane. We went to the site, irradiated the trains for the hospitals, then from this film they analyzed the film, determined the dose and dose rate, and also the homogeneity of the train.

We actually published a paper on the results. The hospitals were very happy with the results, and it came out in the literature about a year ago.

Now, we're also looking into a different method, and that different method is there's another source train in this being calibrated for dose rate and activity. That train will be sent to at least one and probably two accredited dosimetry calibration laboratories, or ADCLs. The ADCL will in turn calibrate their equipment on this train. Then when a hospital wants to know what the dose rate and activity of our trains are, they can simply send their well chamber to the ADCL. It will be calibrated there and returned. And then as often as they wish, they can simply take a source train and put it into the well train to determine activity and dose rate.

So we have here one system that has been proven and has been published in the literature. We have another one that we are working on that should be available quite soon.

DR. AYERS: The latter was what I was really looking for since our anticipated regulations require our licensees to go to an ADCL or NIST for this type of calibration that you just concluded with. So it sounds good.

DR. LOBDEL: Thank you.

DR. AYERS: That's all I have.

ACTING CHAIRPERSON TRACY: That's it? Okay.

Dr. Crittenden, any questions?

DR. CRITTENDEN: Yes, I have several. The first question I'm going to direct to Dr. Speiser and Mr. Green.

What was the impetus behind the device change--the impetus behind the change in the design for the device going from the Alpha III to Alpha IV? Was it to minimize the problems with source delivery? If so, was there a comparison made between these two devices to see if there was a difference.

And then, finally, for this first question, Dr. Speiser stated that the radiation oncologist might feel uncomfortable in the cath lab given that this is a new setting for them and that this may have been a source for some of the source drift or source transit time problems that we saw with the devices.

Is it your position, because the analysis showed that there may be no difference when you look at placebo versus the Strontium-treated groups in terms of outcome, whether you have an MDM or not, is it your position that there are no untoward sequelae for source drift or source transit time?

MR. GREEN: I'll go first, kind of go in order of the questions. The first question I understood to be, you know, what was the reasoning behind going from the Alpha III transfer device to the Alpha IV device. Basically, we started the clinical trial with the Alpha III transfer device. We were having that transfer device manufactured or built by a subcontractor. We moved to another subcontractor, qualified that subcontractor, and part of the qualification of that subcontractor went through for us was to do an evaluation of the Alpha III transfer device and to propose some improvements in the device that may make it more user-friendly, the user interface a little easier to use. And there were several minor things besides the LED.

For instance, the shape of the housing was changed a little better to fit the hand. Some of the graphics were made a little clearer, and the LEDs were added. And the LEDs were added because the subcontractor here determined that they believed that that gave a more accurate feedback than did the mechanism of the Alpha III, which was simply an open window that showed to where you could visualize a spring as part of the pressure relief valve. So they believed this would be a more accurate and calibratable method of providing feedback to the user. And that was the reason we went to that change.

So when we implemented that change, one of the